## REMARKS

In view of the foregoing amendments and the following representations, reconsideration and allowance of the above-identified application is respectfully requested.

Claims 35-46 are pending in the present application.

On page 4 of the Office Action, the Examiner rejected claims 1-4, 7-14, 17-20 and 31-34 under 35 U.S.C. § 103(a) as being unpatentable over the teachings of Cutie et al., WO 01/82875 ("Cutie") in view of Lewis, WO 01/35940 ("Lewis") and further in view of Vergez et al., United States Published Patent Application No. 2006/0204578 ("Vergez").

Applicants have canceled the rejected claims without prejudice. Applicants have submitted new claims 35-46. No new matter is added by these claims. Support can be found in the claims as originally filed and in the Examples 4-6 on pages 18-25 of the specification as filed. Allowance of claims 35-46 is respectfully requested.

New claims 35-46 recite a once a day oral pharmaceutical dosage form that consists essentially of three structural elements: 1) a controlled release metformin core; 2) a primary seal coating surrounding the core; and 3) an immediate release pioglitazone coating applied to the primary seal coating. The use of the term "consisting essentially of" in the preamble of independent claims is intended to indicate the claimed dosage form must employ the three essential elements but may include other elements that do not materially affect the dosage form such as a final aesthetic color coat or polishing coat.

The metformin core must comprise metformin and a semipermeable membrane. The term "consisting essentially of" used to describe the metformin core is intended to

indicate the claimed dosage form must employ the elements recited in the claims and exclude items that materially affect the dosage form such as additional drugs.

Applicants have also included the pioglitazone dissolution profile of prior claims 33 and 34 into the independent claims.

Applicants respectfully submit the pending claims are patentable over the references of record because none of the references of record either alone or combined disclose or suggest to a skilled artisan a once a day metformin/pioglitazone product that employs a semipermeable membrane to control the release of the metformin and an immediate release pioglitazone coating that rapidly releases the pioglitazone with the aid of a primary seal coating between the semipermeable membrane and pioglitazone layer.

In addition, Applicants respectfully submit that dependent claim 39 is patentable over the references of record because none of the references of record either alone or combined disclose or suggest to a skilled artisan a once a day metformin/pioglitazone product that controls the release of the metformin without an expanding (hydrogel) polymer. Similarly, Applicants respectfully submit claims 44-46 are patentable over the references of record because none of the references of record either alone or combined disclose or suggest to a skilled artisan the use of a mixed solvent system to apply the immediate release pioglitazone layer. Applicants have discovered that the mixed solvent system improves application, release and stability of the immediate release pioglitazone layer.

As discussed in the prior submissions, Cutie and Lewis disclose dosage forms that combine metformin and pioglitazone. However, neither of these references discloses the

unique controlled release metformin-immediate release pioglitazone structure recited in the pending claims.

Cutie discloses a "core formulation" with a first layer of pioglitazone. Cutie, page 1, lines 20-24. There is no description of a controlled release metformin core, primary seal coating and immediate release pioglitazone coating as required by the pending claims. In fact, there is no description of an immediate release pioglitazone layer and a semipermeable membrane coated metformin core in Cutie.

Cutie does vaguely suggest a delayed release formulation wherein both the metformin and pioglitazone are coated with a delayed release coating. Specifically, Cutie states:

> The subject core formulation of the invention may contain other various materials which modify the physical form of the dosage unit (the subject core formulation), for example, as coatings. Thus, the subject core formulation of the present invention may be coated with sugar, shellac or other enteric coating agents...
>
> In an alternative embodiment of the present invention. [sic] The resultant core formulation (having a first layer completely or partially covering the core), is treated whereby an outer shell, at least a portion of which comprises a biodegradable material having a predetermined rate of degradation or metabolism in the host being treated, is formed which encloses the particles of the first layer and/or the core....
>
> ...The resulting core formulation having the first layer encapsulated by the shell comprising the shell material, is one which provides a delay time prior to release of the active ingredients, i.e. pioglitazone hydrochloride and metformin, to the patient being treated for diabetes mellitus.

Page 7, line 7 to page 8, line 14 of Cutie. This general description only provides a very broad suggestion of delayed release dosage forms. It does not describe controlled release metformin dosage forms and, more importantly, controlled release metformin dosage

forms wherein a semipermeable membrane controls the release of metformin.

In addition, this general description in Cutie of delayed release dosage forms would lead a skilled artisan to coat both the metformin and pioglitazone with an acid resistant enteric coating, thereby delaying the release of both the metformin and pioglitazone from the dosage form.

The pending claims clearly indicate a rapid release of pioglitazone in an acidic medium. Specifically, the independent claims require a release of at least 79% of pioglitazone after 20 minutes in a pH 2.0 medium and at least 95% after 30 minutes. Based upon the vague and general teachings of Cutie, a skilled artisan would not be lead to the present invention which requires a rapid release of pioglitazone in acidic mediums and a controlled release of metformin via a semipermeable membrane.

The addition of Lewis does not overcome the deficiencies of Cutie. Lewis merely teaches an immediate release dosage form containing immediate release forms of both metformin and pioglitazone. There is no mention, disclosure or suggestion of preparing a controlled release metformin core and an immediate release pioglitazone layer as required by the pending claims. Applicants agree with the Examiner's indication that Lewis teaches the use of an "inert barrier layer" between the thiazolidinedione layer and the metformin layer. Lewis, page 1, lines 38-39. This disclosure, when added to the Cutie teaching, merely suggests to the skilled artisan that an inert barrier layer may be present in the "core formulation" to separate the first pioglitazone layer from the core. This disclosure in Lewis does not motivate or lead an individual of ordinary skill in the art to modify the enteric coated metformin/pioglitazone "core formulation" of Cutie to arrive

at the present invention.

At best, the addition of Lewis merely leads a skilled artisan to insert an inert barrier between the metformin core and first pioglitazone layer of Cutie followed by the application of an enteric coating to the three layer structure. Lewis provides no motivation to modify the Cutie dosage form by surrounding the metformin core with a semipermeable membrane, applying a rapidly dissolving primary seal coating to the semipermeable membrane and applying an immediate release pioglitazone coating to the primary seal coating as required by the pending claims.

The addition of Vergez to Cutie and/or Lewis also would not lead a skilled artisan to the presently claimed invention. Vergez teaches a dual osmotic dosage form that releases two different drugs in a controlled release manner. *See*: Vergez, ¶ 2 ("This invention pertains to a dosage form that provides a controlled release of two different drugs."); ¶ 15 ("The present invention provides an oral dosage form that provides a controlled release device of two or more different active agents"); ¶ 70 ("Neither one of the compositions in the core is intended for rapid release of active agent"); and ¶ 73 ("Neither of the first or second active agents is released rapidly from the core"). The dual controlled release dosage form of Vergez is entirely different from the presently claimed invention.

The present claims require only the metformin to be released in a controlled manner. This limitation is clear from the use of the transition phase "consisting essentially of" to describe the metformin core and the pioglitazone dissolution profile in each claim wherein at least 95% of the pioglitazone must release within 30 minutes.

Therefore, it is respectfully submitted that the addition of Vergez to Cutie and/or Lewis would not lead the skilled artisan to the present invention but rather to metformin/pioglitazone dosage forms that release both drugs in a controlled or delayed manner.

Applicants respectfully submit that the combined teachings of Cutie, Lewis and Vergez would not lead an individual of ordinary skill to the dosage form recited in the pending claims.

On page 12 of the Office Action, the Examiner maintained the provisional non-statutory obviousness-type double patenting rejection of claims based upon co-pending Application No. 11/094,493.

Because Application No. 11/094,493 is currently pending and the claims may be further amended during prosecution, Applicants believe it is premature to submit a terminal disclaimer at the present time. Applicants will consider submitting a terminal disclaimer if allowable subject matter is found in the present application and pending Application No. 11/094,493.

Applicants also respectfully traverse the provisional double patenting rejection because it is believed that the provisions of MPEP § 804(I)(B)(1) should allow the claims of the present application to issue without the submission of a terminal disclaimer. MPEP § 804(I)(B)(1) instructs that a provisional double patenting rejection should be withdrawn if it is the only remaining rejection in an earlier filed application, such as the present situation. Based upon the undisputed facts that the present application was filed before Application No. 11/094,493 and that Application No. 11/094,493 is still pending,

Applicants respectfully request the provisional double patenting rejection be withdrawn in accordance with the provisions of MPEP § 804(I)(B)(1).

Based upon the foregoing amendments and representations, Applicants respectfully requested that the rejection of the claims in the above-identified application be withdrawn. Early and favorable action is earnestly solicited.

Respectfully submitted,

/matthew j. solow/

Matthew J. Solow
Reg. No. 56,878

**MAILING ADDRESS:**
HEDMAN & COSTIGAN, P.C.
1185 Avenue of the Americas
New York, NY 10036-2646
(212) 302-8989